REMARKS

I. Introduction

In response to the Office Action dated March 15, 2004, claims 55-57 has been added. Claims 28-30, 48-50, 54 and 55-57 remain in the application. Re-examination and re-consideration of the application is requested.

At page 2 of the Office Action, the Examiner requested additional information regarding Exhibit "C" submitted with the response of 12/9/2003 (pages 242-252 of FUNDAMENTAL IMMUNOLOGY [3rd. Ed. Raven Press]). This information is provided herein as Attachment A.

II. Objections and Rejections Under 35 U.S.C. §101 and 35 U.S.C. §112, First Paragraph

On pages 2-6 of the Office Action, claims 28-30, 48-50 and 54 were rejected under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

A. Claims Rejected Under 35 U.S.C. §101.

The pending claims are directed to isolated antibodies which bind to a PRO285 polypeptide, a member of the Toll protein family.

Applicants' disclosure teaches that comparative homology analyses and functional data from Toll family members indicate that PRO285 polypeptide signalling activates NF-κB, an event which leads to the expression of the inflammatory cytokines IL-1, IL-6 and IL-8. See, e.g. page 13, lines 13-25. Applicants' disclosure further teaches that antibodies to the PRO285 polypeptide can act as agonists or antagonists of NF-κB signalling and can therefore be used in methods designed to modulate the expression of genes controlled by NF-κB. See, e.g. page 13, lines 6-25.

As is known in the art, methods designed to modulate the expression of IL-1, IL-6 and IL-8 (e.g. via NF-κB activation) can be used in a variety of contexts. For example, reagents which induce the expression of IL-1, IL-6 and IL-8 are used in the topical treatment of warts (see, e.g. Beutner et al., Am. J. Med. 102 (5A) 28-37 (1997), a copy of which is provided as Attachment B). The specification further teaches that antagonistic anti-PRO285 antibodies may be used in pathologies characterized by an overexpression of IL-1, IL-6 and IL-8 (i.e. septic shock). See, e.g., page 37, lines 10-29. Consequently, one of skill in the art is familiar with circumstances where it is desirable to either stimulate or inhibit the activities mediated by PRO285.

In support of their asserted utility, Applicants provided a declaration under 37 CFR 1.1.32 by J. Fernando Bazan which states that one skilled in the art would reasonably understand that PRO285 can induce the expression of NF-κB-controlled genes and that antibodies to PRO285 can be made and used in accordance with routine techniques to modulate such activity. The utility of the claimed subject matter is further validated by recent reports which confirm that molecules that bind to PRO285 can be used to modulate the expression of NF-κB-controlled genes. See e.g. Jurk et al., Nature Immunology 3(6), 499 (2002), a copy of which was provided with the response dated 12/9/2003.

In the outstanding Office Action, the Examiner rejects the pending claims, stating that the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility.

Applicants respectfully traverse this rejection because the utility asserted for the claimed subject matter would be considered specific, substantial and credible by the skilled artisan. For example, the use of agonistic and antagonistic antibodies as reagents to modulate the biological activities of a target receptor molecule is well known practice in the art. It is also known in the art that NF-κB controls the expression of IL-1, IL-6 and IL-8, cytokines whose aberrant expression is observed in a number of pathological syndromes including septic shock. While the association of PRO285 with NF-κB activation is based on a homology analysis, this technique is an art accepted method which is specifically designed to identify functional relationships based upon similarities in amino acid sequences. In support of the homology analysis and the asserted utility, Applicants provided an opinion of a qualified expert stating that one of skill in the art would find credible Applicants teaching that PRO285 can induce the expression of that IL-1, IL-6 and IL-8 (NF-κB-controlled genes) and that antibodies to PRO285 can be made and used in accordance with routine techniques to modulate the expression of these inflammatory cytokines. In addition, as noted above, the Jurk et al. reference teaches that PRO285 binding molecules do in fact modulate the expression of NF-κB-controlled genes.

While the Examiner asserts a lack of a substantial utility because "mere signaling via NF-κB would not be indicative of utility", Applicants respectfully disagree because artisans do in fact understand the usefulness of methods which modulate the expression of IL-1, IL-6 and IL-8, cytokines whose aberrant expression is observed in a number of pathological syndromes including

septic shock (as described at page 6, lines 9-12). While the Examiner also asserts that the specification fails to teach how anti-receptor antibodies can modulate receptor activity (i.e. PRO285 activity), Applicants note that (as described at page 13, lines 6-25) the use of antibodies in such methods is well known in the art and would be considered credible by the skilled artisan. Moreover, while the Examiner disputes the expert's opinion, arguing for example that "of the six essential residues for IL-R1 signaling domain, only two are conserved in PRO285", Applicant's once again point out that the expert's opinion on the significance of the homology is in fact correct as shown by the disclosure in Jurk et al. (which teaches that PRO285 binding molecules do in fact modulate the expression of NF-κB-controlled genes). While the issue is indisputable in view of the disclosure of Jurk et al., Applicants further note that the guidelines state that office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned (section 4 of the guidelines promulgated by the Patent Office).

As noted above, the utility asserted for the claimed subject matter: (1) is readily understood by a skilled artisan; (2) conforms to known principles in this art; and (3) is acknowledged in opinion from a qualified expert. Consequently, the asserted utility would be considered credible by a person of ordinary skill in the art. In the instant situation, the Patent Office does not meet the requisite burden of proving that one of ordinary skill in the art would doubt the asserted utility. In particular, the guidelines promulgated by the Patent Office for the examination of applications for compliance with the utility requirement of 35 USC 101 and 35 USC 112, first paragraph dictate that if the assertion would be considered credible by a person of ordinary skill in the art, the Patent Office **must not** impose a rejection based on lack of utility. Only after an examiner has provided evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the Applicants (see, e.g. M.P.E.P. 2164.07). In the instant case, the PTO fails to meet this burden. For at least the reasons above, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. §101.

B. Rejection under 35 U.S.C. §112, First Paragraph.

In rejecting the claims under 35 U.S.C. §112 at page 4 of the outstanding office action the Examiner further asserts "since the claimed invention is not supported by either a specific,

substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention."

Those of skill in the art will understand from the instant application and the state of the art that Applicants' invention has a specific, substantial and credible asserted utility. Consequently, one skilled in the art clearly would in fact know how to use the claimed invention without undue experimentation. For this reason, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. §112 first paragraph.

III. Rejection under 35 U.S.C. §102(b)

On pages 6-7 of the Office Action, claims 28 and 48 were rejected under 35 U.S.C. §102(b) as being anticipated by Ruggeri et al., WO 91/09614 (Ruggeri). The Examiner asserts that Ruggeri et al. disclose a 19 residue platelet membrane glycoprotein Ib peptide that matches SEQ ID NO: 2 at positions 704-712, a 9/15 amino acid residue match and that at page 19 and in claim 65, antibodies to such peptides are disclosed and claimed. The Examiner acknowledges that this is anticipation via inherency and that "[I]t is not necessary that Ruggeri have any knowledge of PRO285 for anticipation to be found" (see, e.g. page 5 of paper # 22).

In their response to the previous office action Applicants noted that although PRO 285 and platelet membrane glycoprotein Ib share a common 9 amino acid sequence, the topography of the antigenic determinant formed by the 19 residue platelet membrane glycoprotein Ib peptide is not necessarily reproduced in the PRO285 polypeptide recited in the claims. Consequently, an antibody specific for the 19 residue platelet membrane glycoprotein Ib peptide will not necessarily bind the PRO285 polypeptide. In the instant Office Action, the Examiner acknowledges this, stating that the Ruggeri disclosure anticipates the claimed subject matter because "one would reasonably expect an antibody raised against Ruggeri's peptide to bind to PRO285".

Applicants respectfully traverse this rejection because it is contrary to the legal requirements for a finding of anticipation. In particular, when articulating the legal requirements for a finding of anticipation via inherency, courts state that inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." See, e.g. M.P.E.P. 2112 and *Continental Can Co. v. Monsanto Co.*, 20 USPQ 2d 1746, 1749 (Fed. Cir. 1991). Instead, to establish inherency, the extrinsic evidence "must make clear that the

missing descriptive matter is **necessarily present** in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co.*, 20 USPQ 2d 1749.

The outstanding rejection is explicitly predicated on a probability, i.e. that one would "reasonably expect" an antibody raised against a platelet membrane glycoprotein Ib peptide to crossreact with a PRO285 polypeptide. The outstanding rejection is not based on a showing that the claimed subject matter is in fact necessarily present in the Ruggeri disclosure. Consequently this rejection is contrary to the requirements for a finding of anticipation via inherency (e.g. as articulated in *Continental Can Co. v. Monsanto Co.*, 20 USPQ 2d at 1749). For this reason, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. §102(b).

IV. Rejection under 35 U.S.C. §103(a)

At page 7 of the Office Action, claim 51 was rejected under 35 U.S.C. §103(a) as being unpatentable over Ruggeri in view of Coughlin, U.S. Patent No. 5,256,766 (Coughlin), and further in view of Ladner et al., U.S. Patent No. 4,946,778 (Ladner).

As the Ruggeri disclosure fails to meet the legal requirements for anticipation via inherency, this reference cannot properly be combined with U.S. Patent No. 5,256,766 and U.S. Patent No. 4,946,778 in order to suggest the subject matter recited in claim 52. For this reason, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. 103(a).

V. Conclusion

In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

Respectfully submitted,

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